

bioinformatics tools."

In the Claims

Please amend claims 1-12 under the provisions of 37 C.F.R. §1.121(b) by deleting the bracketed material and inserting the underlined material as follows:

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--1. (Amended) A system for [pan-genomic determination of] determining experimentally a plurality of three-dimensional [macromolecular] atomic structures, each of which is associated with a corresponding protein, comprising:

[database means for systematically organizing all known structural information into] a [genomics] database of sequence information, and known structural information [, sequence information] and functional information, which is systematically organized for a plurality of proteins;

at least one bioinformatics [means for] tool using [said] the structural information, sequence information and functional information stored in [said] the database to cluster [a] the plurality of [known gene products] proteins into a plurality of families, in which members of each family have corresponding [of] homologous sequences;

protein synthesis means for synthesizing for each family determined by the at least one bioinformatics tool, in parallel [simultaneously], a plurality of [member] target proteins, which are appropriately representative members of the family, using [genomics] information [of a plurality of appropriately representative species;] stored in the database corresponding to the target proteins, the protein synthesis means having screening means for screening the [synthesized proteins] products of the synthesis to determine ones that are effective as proteins;

protein processing means for preparing, purifying and characterizing [the screened proteins] each target protein which is determined to be effective by [said] the screening means;

crystallization means for crystallizing [a plurality of the

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purified proteins] each target protein processed by the protein processing means in parallel against a plurality of crystallization screens to produce a plurality of specimen crystals of the target protein, and testing [a] the plurality of [grown] specimen crystals for predetermined diffraction characteristics to determine suitable ones of [said] the plurality of [grown] specimen crystals of the target protein;

X-ray crystallography means for performing high-throughput crystallography on the specimen crystals of each target protein determined by the crystallization means to be suitable, [said] the X-ray crystallography means having diffraction measuring means for measuring [a suitable crystal] for diffraction data the suitable specimen crystals of the target protein, analyzing means for analyzing [said] the diffraction data, means for building an atomic model of the target protein according to an analysis of the diffraction data by the analyzing means, and means for refining [said] the model of the target protein against [said] the diffraction data and storing the refined model in [said] the database;

structure extraction means having means for analyzing the refined model of the target protein using sequence information [of] corresponding to other family members which is stored in the database and information [of] corresponding to other known three-dimensional structures which is stored in the database, means for analyzing the refined model for functional motifs and for surface characteristics to define active sites and macromolecular contact sites, and means for defining at least one class of compounds predicted to have binding potency using the active sites information corresponding to the target protein; and

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a homology model building [means for] tool developing a homology model using [an atomic] the refined model of the target protein retrieved from [said] the database,

wherein [an ensemble of all known structures is used to further advance an effectiveness of said] the database is updated using the at least one bioinformatics [means] tool along with the

developed homology model.--

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--2. (Amended) A system according to claim 1, further comprising:

cryoprotection means for freezing [said] the suitable ones of [said] the plurality of specimen crystals of the target protein which are [supplied] determined to be suitable by [said] the crystallization means,

wherein [said] the specimen crystals determined by the crystallization means to be suitable [crystal is] are frozen by [said] the cryoprotection means before being measured for [said] diffraction data by [said] the diffraction measuring means.--

--3. (Amended) A system according to claim 1, wherein

[said] the protein synthesis means includes cloning means for cloning for [said] each family determined by the at least one bioinformatics tool, in parallel [simultaneously], cDNAs [of said plurality of] corresponding to the appropriately representative [species] family members into a plurality of expression vectors for a plurality of expressions systems,

[said] the screening means screens for expression constructs obtained [from said] by the cloning means to determine ones that are effective as proteins, and

[said] the protein processing means processes the expressed proteins determined to be effective by [said] the screening means.--

--4. (Amended) A system according to claim 1, wherein

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[said] the X-ray crystallography means includes a synchrotron storage ring having undulator beamlines for high-throughput crystallography by a multiwavelength anomalous diffraction method, and

[said] the analyzing means analyzes [said] the diffraction data by a multiwavelength anomalous diffraction phasing method.--

--5. (Amended) A system according to claim 4, wherein selenomethionine is incorporated in the synthesized target proteins by [said] the protein synthesis means, and [said] the analyzing means using [said] the multiwavelength anomalous diffraction phasing method analyzes [said] diffraction data [of] corresponding to selenomethionyl proteins.--

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--6. (Amended) A system according to claim 1, wherein [said] the homology model developed by the homology model building tool is used in at least one of target selection, drug design, and design of more appropriate constructs for experimental analysis.--

--7. (Amended) A process for [pan-genomic determination of] determining experimentally a plurality of three-dimensional [macromolecular] atomic structures, each of which is associated with a corresponding protein, comprising the steps of:

(a) systematically organizing [all] sequence information, and known structural information [, sequence information] and functional information, for a plurality of proteins into a [genomics] database;

(b) clustering [a] the plurality of [known gene products] proteins into a plurality of families [of], in which members of each family have corresponding homologous sequences, using at least one bioinformatics [tools] tool and the sequence information, structural information and functional information stored in the database;

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(c) synthesizing for each family determined in step (b), in parallel [simultaneously], a plurality of [member] target proteins, which are appropriately representative members of the family, using [genomics] information [of a plurality of appropriately representative species;] stored in the database corresponding to the plurality of target proteins, and screening [the synthesized proteins] products of the synthesis to determine ones that are effective as proteins;

(d) preparing, purifying and characterizing [the screened

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proteins] each target protein which is determined to be effective in [said] step [of screening] (c);

(e) crystallizing [a plurality of purified proteins] each target protein prepared, purified and characterized in step (d) in parallel against a plurality of crystallization screens to produce a plurality of specimen crystals of the target protein;

(f) testing [a] the plurality of [grown] specimen crystals of one of the target proteins grown in step (e) for predetermined diffraction characteristics to determine suitable ones of [said] the plurality of [grown] specimen crystals of the one target protein;

(g) performing high-throughput crystallography, including measuring [a suitable crystal] for diffraction data the specimen crystals of the one target protein determined in step (f) to be suitable, [build] building an atomic model of the one target protein according to an analysis of [said] the diffraction data, refining [said] the model of the one target protein against [said] the diffraction data, and storing the refined model in [said] the database;

(h) analyzing the refined model, stored in the database in step (g), of the one target protein using sequence information [from] corresponding to other family members which is stored in the database and information [of] corresponding to other known three-dimensional structures which is stored in the database, analyzing the refined model of the one target protein for functional motifs and for surface characteristics to define active sites and macromolecular contact sites, and defining at least one class of compounds predicted to have binding potency using the active sites information corresponding to the one target protein; [and]

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(i) developing a homology model using computational tools for homology model building and [an atomic] the refined model of the one target protein retrieved from [said] the database, [wherein said] and updating the database [is updated] by using [said] the at least one bioinformatics [tools] tool along with

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[said all known structural information and an ensemble of all known structures is used to further advance an effectiveness of said bioinformatics tools] the developed homology model; and
(j) performing steps (f) through (i) for each of the other target proteins.--

--8. (Amended) A process according to claim 7, further comprising the step of:

freezing [selected] the suitable ones of [said] the plurality of [grown] specimen crystals of the one target protein which are determined in step (f) to be suitable [in said step of testing],

wherein [said suitable crystal is] the plurality of specimen crystals determined to be suitable are frozen before being measured for [said] the diffraction data in [said] step [of measuring] (g).--

--9. (Amended) A process according to claim 7, wherein

[said] step [of synthesis] (c) includes [the step of] cloning for [said] each family determined in step (b), in parallel [simultaneously], cDNAs [from said plurality of] corresponding to the appropriately representative [species] family members into a plurality of expression vectors for a plurality of expressions systems,

constructs obtained in [said step of] the cloning are screened for expression to determine the ones that are effective as proteins, and

the expressed proteins determined to be effective are processed in [said] step [of preparing, purifying and characterizing] (d).--

--10. (Amended) A process according to claim 7, wherein

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[said] the high-throughput crystallography in step (g) is performed using a synchrotron storage ring having undulator beamlines along with a multiwavelength anomalous diffraction